**FINAL PROFESSIONAL INFORMATION**

**SCHEDULING STATUS**

**S4**

**1. NAME OF THE MEDICINE**

**IMATINIB ACCORD 100** (film-coated tablets)

**IMATINIB ACCORD 400** (film-coated tablets)

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

**IMATINIB ACCORD 100**: Each film-coated tablet contains imatinib mesylate equivalent to 100 mg imatinib

**IMATINIB ACCORD 400**: Each film-coated tablet contains imatinib mesylate equivalent to 400 mg imatinib

Sugar free.

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Film coated tablets.

**IMATINIB ACCORD 100**: Brownish orange, round, biconvex, film-coated tablets, debossed with 'IM' and 'T1' on either side of the score and plain on the other side.

**IMATINIB ACCORD 400**: Brownish orange, oval shaped, biconvex, film-coated tablets, debossed with 'IM' and 'T2' on either side of the score and plain on the other side.

**4. CLINICAL PARTICULARS**

**4.1 THERAPEUTIC INDICATIONS**

- Adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (CML).
- Adult and paediatric patients with CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

- Adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.
- Adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- Adult patients with systemic mastocytosis (SM) without the D816V c-Kit mutation and eosinophilia.
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.
- Adult patients with unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

## 4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Therapy should be initiated by a medical practitioner experienced in the treatment of patients with chronic myeloid leukaemia or GIST respectively.

### Adult Dosage in CML

The recommended dosage of **IMATINIB ACCORD** is 400 mg daily for patients in chronic phase CML and 600 mg daily for patients in accelerated phase or blast crisis. Treatment should be continued as long as the patient continues to benefit.

Dose increase from 400 mg to 600 mg or to 800 mg in patients with chronic phase disease, or from 600 mg to a maximum of 800 mg (given as 400 mg twice daily) in patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reactions and severe non-leukaemia-related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory haematological response after at least 3 months of treatment; failure to achieve a cytogenic response after 12 months or treatment; or loss of a previously achieved haematological response and/or cytogenic response.

### Dosage for CML in children

Dosing in children should be on the basis of body surface area (mg/m$^2$). The dose 340 mg/m$^2$ daily is recommended

for children with chronic phase CML and advanced phase CML (not to exceed the total dose of 600 mg daily). Treatment can be given as a once daily dose or alternatively the daily dose may be split into two administrations – one in the morning and one in the evening. There is no experience with the use of **IMATINIB ACCORD** in children under the age of 2 years.

**Dosage in Ph+ ALL**

The recommended dose of **IMATINIB ACCORD** is 600 mg daily for patients with Ph+ ALL.

**Dosage in MDS/MPD**

The recommended dose of **IMATINIB ACCORD** is 400 mg daily for patients with MDS/MPD.

**Dosage in SM**

For patients with SM associated with eosinophilia, a clonal haematological disease related to the fusion kinase FIP1L1-PDGFRa, a starting dose of 100 mg daily is recommended. A dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

**Dosage in HES/CEL**

For HES/CEL patients with demonstrated FIP1L1-PDGFRa fusion kinase, a starting dose of 100 mg daily is recommended. A dose increase from 100 mg to 400 mg for these patients may be considered in the absence of side effects if assessments demonstrate an insufficient response to therapy.

**Dosage in GIST**

The recommended dose of **IMATINIB ACCORD** is 400 mg daily for patients with unresectable and/or metastatic, malignant GIST. A dose increase from 400 mg to 600 mg or 800 mg for patients may be considered in the absence of side effects if assessments demonstrate an insufficient response to therapy.

Treatment with **IMATINIB ACCORD** in GIST patients should be continued until disease progression.

**Dosage in DFSP**

The recommended dose of **IMATINIB ACCORD** is 800 mg daily for patients with DFSP.

**Dose adjustments for side effects**

*Non-haematological side effects:*

If a severe non-haematological side effect develops with **IMATINIB ACCORD** use, treatment must be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.

If elevations in bilirubin > 3 x institutional upper limit of normal (IULN) or in liver transaminases > 5 x IULN occur, **IMATINIB ACCORD** should be withheld until bilirubin levels have returned to a < 1,5 x IULN and transaminase levels to < 2,5 x

IULN. Treatment with **IMATINIB ACCORD** may then be continued at a reduced daily dose. In adults the dose should be reduced from 400 to 300 mg or from 600 to 400 mg, or from 800 mg to 600 mg and in children from 340 to 260 mg/$m^2$ daily.

*Haematological side effects:*

Dose reduction or treatment interruption for severe neutropenia and thrombocytopenia are recommended as indicated in the table below.

**Dose adjustments for neutropenia and thrombocytopenia:**

| | | |
|---|---|---|
| SM associated with eosinophilia and HES/CEL with FIP1L1-PDGFRα fusion kinase (starting dose 100 mg) | ANC < 1,0 x $10^9$/l and/or platelets < 50 x $10^9$/l | 1. Stop **IMATINIB ACCORD** until ANC ≥ 1,5 x $10^9$/l and platelets ≥ 75 x $10^9$/l.<br>2. Resume treatment with **IMATINIB ACCORD** at previous dose (i.e. before severe side effect). |

| | | |
|---|---|---|
| Chronic phase CML, MDS/MPD, SM, HES/CEL and GIST (starting dose 400 mg) | ANC < 1,0 x $10^9$/l and/or platelets < 50 x $10^9$/l | 1. Stop **IMATINIB ACCORD** until ANC ≥ 1,5 x $10^9$/l and platelets ≥ 75 x $10^9$/l.<br>2. Resume treatment with **IMATINIB ACCORD** at previous dose (i.e. before severe side effect).<br>3. In the event of recurrence of ANC < 1,0 x $10^9$/l and/or < 50 x $10^9$/l, repeat step 1 and resume **IMATINIB ACCORD** at reduced dose of 300 mg. |
| Paediatric chronic phase CML (at dose 340 mg/$m^2$) | ANC < 1,0 x $10^9$/l and/or platelets < 50 x $10^9$/l | 1. Stop **IMATINIB ACCORD** until ANC ≥ 1,5 x $10^9$/l and platelets ≥ 75 x $10^9$/l.<br>2. Resume treatment with **IMATINIB ACCORD** at previous dose (i.e. before severe side effect).<br>3. In the event of recurrence of ANC < 1,0 x $10^9$/l and/or < 50 x $10^9$/l, repeat step 1 and resume **IMATINIB ACCORD** at reduced dose of 260 mg. |
| Accelerated phase CML and blast crisis and Ph+ ALL (starting dose 600 mg [c]) | [a]ANC < 0,5 x $10^9$/l and/or platelets < 10 x $10^9$/l | 1. Check whether cytopenia is related to leukaemia (marrow aspirate or biopsy).<br>2. If cytopenia is unrelated to |

| | | |
|---|---|---|
| | | leukaemia, reduce dose of **IMATINIB ACCORD** to 400 mg [b].<br>3. If cytopenia persists for *2* weeks, reduce further to 300 mg [d].<br>4. If cytopenia persists for 4 weeks and is still unrelated to leukaemia, stop **IMATINIB ACCORD** until ANC 1,0 x $10^9$/l and platelets ≥ 20 x $10^9$/l, then resume treatment at 300 mg [d]. |
| DFSP (starting dose 800 mg) | ANC < 1,0 x $10^9$/l and/or platelets < 50 x $10^9$/l | 1. Stop **IMATINIB ACCORD** until ANC ≥ 1,5 x $10^9$/l and platelets ≥ 75 x $10^9$/l.<br>2. Resume treatment with **IMATINIB ACCORD** at 600 mg<br>3. In the event of recurrence of ANC < 1,0 x $10^9$/l and/or < 50 x $10^9$/l, repeat step 1 and resume **IMATINIB ACCORD** at reduced dose of 400 mg. |

ANC = absolute neutrophil count

[a] Occurring after at least 1 month of treatment

[b] 260 mg/$m^2$ in children

[c] 340 mg/$m^2$ in children

[d] 200 mg/$m^2$ in children.

**Special Populations:**

*Children*

There is very limited experience with the use of **IMATINIB ACCORD** in children for other indications.

*Hepatic insufficiency*

**IMATINIB ACCORD** is mainly metabolised through the liver. Patients with mild, moderate or severe liver dysfunction should be given the minimum recommended dose of 400 mg daily. The dose can be reduced if the patient develops unacceptable toxicity (see section 4.4 and 5.2).

*Renal insufficiency*

Imatinib and its metabolites are not significantly excreted via the kidney. However, in severe renal insufficiency caution is recommended. Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as a starting dose. The dose can be reduced if not tolerated. If tolerated it can be increased for lack of efficacy.

*Elderly patients*

No specific dose recommendation is necessary in the elderly.

**Method of administration**

The prescribed dose should be administered orally, once daily with a meal and a large glass of water, to minimize the risk of gastrointestinal disturbances. Doses of 400 mg or 600 mg should be administered once daily, whereas a daily dose of 800 mg should be administered as 400 mg twice a day, in the morning and in the evening.

For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 ml for a 100 mg tablet, and 200 ml for a 400 mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

**4.3 CONTRAINDICATIONS**

Hypersensitivity to imatinib, the metabolite N-demethylated piperazine derivative, or to any of the inactive ingredients of **IMATINIB ACCORD** listed in section 6.1.

Pregnancy and lactation (see section 4.6).

**4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

When **IMATINIB ACCORD** is co-administered with other medications, there is a potential for drug interactions (see section 4.5).

Caution should be exercised when taking **IMATINIB ACCORD** with protease inhibitors, azole antifungals, certain macrolides (see section 4.5), CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel, quinidine) or warfarin and other coumarin derivatives (see section 4.5).

Concomitant use of imatinib and medicines that induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or Hypericum perforatum, also known as St. John's Wort) may significantly reduce exposure to imatinib, potentially increasing the risk of therapeutic failure. Therefore, concomitant use of strong CYP3A4 inducers and imatinib should be avoided (see section 4.5).

Patients with cardiac disease

Patients with cardiac disease, risk factors for cardiac failure or history of renal failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac or renal failure should be evaluated and treated.

In patients with HES with occult infiltration of HES cells within the myocardium, isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with HES cell degranulation upon the initiation of imatinib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding **IMATINIB ACCORD**. Myelodysplastic/myeloproliferative diseases and systemic mastocytosis might be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD or SM associated with high eosinophil levels. If either is abnormal, the prophylactic use of systemic steroids (1 – 2 mg/kg) for one to two weeks concomitantly with **IMATINIB ACCORD** should be considered at the initiation of therapy.

Hepatotoxicity

Metabolism of imatinib is mainly hepatic, only 13 % is through the kidneys. In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored (see sections

4.2, 4.8 and 5.2). It should be noted that GIST patients may have hepatic metastases which could lead to hepatic impairment.

Cases of liver injury, including hepatic failure and hepatic necrosis have been reported with imatinib. When **IMATINIB ACCORD** is combined with high dose chemotherapy regimens, transient liver toxicity in the form of transaminase elevation and hyperbilirubinaemia can be observed. Monitoring of liver function is recommended in circumstances where **IMATINIB ACCORD** is combined with chemotherapy regimens also known to be associated with hepatic dysfunction (see sections 4.5 and 4.8).

Fluid retention

Occurrences of severe fluid retention (pleural effusion, oedema, pulmonary oedema, superficial oedema and ascites) have been reported in approximately 2,5 % of newly diagnosed CML patients taking imatinib. Therefore, it is recommended that patients be weighed regularly.

An unexpected rapid weight gain should be carefully investigated and if necessary appropriate supportive care and therapeutic measures should be undertaken. In clinical trials, there was an increased incidence of these events in elderly and cardiac patients. Therefore, caution should be exercised in patients with cardiac dysfunction.

Gastrointestinal haemorrhage

In GIST patients, gastrointestinal (GI) haemorrhage and haemorrhages at the site of tumours were reported (see section 4.8). Patients should therefore be monitored for gastrointestinal symptoms at the start of therapy.

No predisposing factors (e.g. tumour size, tumour location, coagulation disorders) have been identified that place patients with GIST at a higher risk of either type of haemorrhage.

Since increased vascularity and propensity for bleeding is a part of the nature and clinical course of GIST, standard practices and procedures for the monitoring and management of haemorrhage in all patients should be applied.

In addition, gastric antral vascular ectasia (GAVE), a rare cause of gastrointestinal haemorrhage, has been reported in patients with CML, ALL and other diseases (see section 4.8). When needed, discontinuation of imatinib treatment may be considered.

Tumour lysis syndrome

Due to the possible occurrence of tumour lysis syndrome (TLS), correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of **IMATINIB ACCORD** (see section 4.8).

Hypothyroidism

Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with imatinib (see section 4.5). Thyroid-stimulating hormone (TSH) levels should be closely monitored in such patients.

Laboratory tests

Complete blood counts must be performed regularly during therapy with **IMATINIB ACCORD**. Treatment of CML patients with **IMATINIB ACCORD** has been associated with neutropenia or thrombocytopenia. However, the occurrence of these cytopenias is dependent on the stage of the disease being treated and they were more frequent in patients with accelerated phase CML or blast crisis as compared to patients with chronic phase CML. Treatment with **IMATINIB ACCORD** may be interrupted or the dose may be reduced, as recommended under section 4.2.

Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored regularly in patients receiving **IMATINIB ACCORD**. As recommended under section 4.2, Non-haematological adverse reactions, these laboratory abnormalities should be managed with interruption and/or dose reduction of the treatment with **IMATINIB ACCORD.**

**IMATINIB ACCORD** and its metabolites are not excreted via the kidney to a significant extent. Creatinine clearance is known to decrease with age, and age did not significantly affect **IMATINIB ACCORD** kinetics.

In patients with impaired renal function, imatinib plasma exposure seems to be higher than that in patients with normal renal function, probably due to an elevated plasma level of alpha-acid glycoprotein (AGP), an imatinib-binding protein, in these patients. Patients with renal impairment should be given the minimum starting dose. Patients with severe renal impairment should be treated with caution. The dose can be reduced if not tolerated (see section 4.2). Long-term treatment with imatinib may be associated with a clinically significant decline in renal function. Renal function should, therefore, be evaluated prior to the start of imatinib therapy and closely monitored

during therapy, with particular attention to those patients exhibiting risk factors for renal dysfunction. If renal dysfunction is observed, appropriate management and treatment should be prescribed in accordance with standard treatment guidelines.

Hepatitis B reactivation

Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL tyrosine kinase inhibitors. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Patients should be tested for HBV infection before initiating treatment with **IMATINIB ACCORD**. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with Imatinib Accord should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Class effects of Tyrosine Kinase Inhibitors (TKIs) such as contained in Imatinib Accord

Cases of cerebrovascular accident, transient ischaemic attack, and ischaemic stroke including fatalities have been reported with the use of TKIs such as imatinib, with or without concomitant atrial fibrillation and/or hypertension, although causality with imatinib has not been established (see section 4.8). Regular monitoring and appropriate treatment of conditions that can contribute to the occurrence of these events, are recommended.

Phototoxicity

Exposure to direct sunlight should be avoided or minimised due to the risk of phototoxicity associated with imatinib treatment. Patients should be instructed to use measures such as protective clothing and sunscreen with high sun protection factor (SPF).

Thrombotic microangiopathy

BCR-ABL tyrosine kinase inhibitors (TKIs) have been associated with thrombotic microangiopathy (TMA) (see section 4.8). If laboratory or clinical findings associated with TMA occur in a patient receiving imatinib, treatment

should be discontinued and thorough evaluation for TMA, including ADAMTS13 activity and anti-ADAMTS13-antibody determination, should be completed. If anti-ADAMTS13-antibody is elevated in conjunction with low ADAMTS13 activity, treatment with imatinib should not be resumed.

Paediatric population

There have been case reports of growth retardation occurring in children and pre-adolescents receiving imatinib. The long-term effects of prolonged treatment with imatinib on growth in children are unknown. Therefore, close monitoring of growth in children under imatinib treatment is recommended (see section 4.8).

**4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION**

**Medicines that may increase IMATINIB ACCORD plasma concentrations**

- Substances that inhibit the cytochrome P-450 isoenzyme CYP3A4 activity (e.g. protease inhibitors such as indinavir, lopinavir/ritonavir, ritonavir, saquinavir, telaprevir, nelfinavir, boceprevir; azole antifungals including ketoconazole, itraconazole, posaconazole, voriconazole; certain macrolides such as erythromycin, clarithromycin and telithromycin) could decrease metabolism and increase **IMATINIB ACCORD** concentrations. There was a significant increase in exposure to imatinib (the mean $C_{max}$ and AUC of imatinib rose by 26 % and 40 %, respectively) in healthy subjects when it was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor). Caution should be taken when administering **IMATINIB ACCORD** with inhibitors of the CYP3A4 family.

**Medicines that may decrease IMATINIB ACCORD plasma concentrations**

- Substances that are inducers of CYP3A4 activity could increase metabolism and decrease **IMATINIB ACCORD** plasma concentrations. Co-medications which induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, fosphenytoin, primidone or *Hypericum perforatum* (also known as St John's Wort) may significantly reduce exposure to **IMATINIB ACCORD,** potentially increasing the risk of therapeutic failure. Caution should be taken when administering **IMATINIB ACCORD** with inhibitors of CYP3A4. Concomitant use of rifampicin or other strong CYP3A4 inducers and imatinib should be avoided.

**Medicines that may have their plasma concentration altered by IMATINIB ACCORD**

- **IMATINIB ACCORD** increases the mean $C_{max}$ and AUC of simvastatin (CYP3A4 substrate) 2- and 3,5-fold, respectively, indicating an inhibition of the CYP3A4 by **IMATINIB ACCORD**. Therefore, caution is recommended when administering **IMATINIB ACCORD** with CYP3A4 substrates with a narrow therapeutic window (e.g. ciclosporin, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel and quinidine). **IMATINIB ACCORD** may increase plasma concentrations of other CYP3A4 metabolised medicines (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e. statins, etc.).
- **IMATINIB ACCORD** also inhibits CYP2C9 and CYP2C19 activity *in vitro*. PT prolongation was observed following co-administration with warfarin. When giving coumarins, short-term PT monitoring is therefore necessary at the start and end of **IMATINIB ACCORD** therapy and when altering the dosage. Alternatively, the use of low molecular weight heparin should be considered.
- *In vitro*, **IMATINIB ACCORD** inhibits the cytochrome P-450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. Systemic exposure to substrates of CYP2D6 is therefore potentially increased when co-administered with **IMATINIB ACCORD**. Dose adjustments do not seem to be necessary when imatinib is co-administrated with CYP2D6 substrates, however caution is advised for CYP2D6 substrates with a narrow therapeutic window such as metoprolol. In patients treated with metoprolol clinical monitoring should be considered.
- *In vitro*, imatinib inhibits paracetamol O-glucuronidation with Ki value of 58,5 micromol/l. This inhibition has not been observed *in vivo* after the administration of imatinib 400 mg and paracetamol 1000 mg. Higher doses of imatinib and paracetamol have not been studied. Caution should therefore be exercised when using high doses of **IMATINIB ACCORD** and paracetamol concomitantly.
- In thyroidectomy patients receiving levothyroxine, the plasma exposure to levothyroxine may be decreased when imatinib is co-administered (see section 4.4). Caution is therefore recommended. However, the mechanism of the observed interaction is presently unknown.
- In Ph+ ALL patients, there is clinical experience of co-administering imatinib with chemotherapy (see section 5.1), but interactions between imatinib and chemotherapy regimens are not well characterised. Imatinib adverse events, i.e. hepatotoxicity, myelosuppression or others, may increase and it has been

reported that concomitant use with L-asparaginase could be associated with increased hepatotoxicity (see section 4.8). Therefore, the use of imatinib in combination requires special precaution.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

**IMATINIB ACCORD** should not be taken during pregnancy or lactation (see section 4.3).

Women of childbearing potential must be advised to use highly effective contraception during treatment and for 15 days after stopping treatment to avoid pregnancy.

Use in pregnancy may lead to foetal abortion or malformation. Patients should not breastfeed during treatment. Both imatinib and its active metabolite can be distributed into human milk.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be advised that they may experience undesirable effects such as dizziness, somnolence or blurred vision during treatment with **IMATINIB ACCORD**. Therefore, caution should be recommended when driving a car or operating machinery.

## 4.8 UNDESIRABLE EFFECTS

*Tabulated summary of adverse reactions*

| SYSTEM ORGAN CLASS | FREQUENCY | ADVERSE REACTION |
|---|---|---|
| **Infections and infestations** | Less frequent | Sepsis, pneumonia, herpes simplex, herpes zoster, upper respiratory tract infection, gastroenteritis, sinusitis, cellulitis, influenza, urinary tract infections, nasopharyngitis, fungal infection |
| | Frequency unknown | Hepatitis B reactivation* |
| **Neoplasm benign, malignant and unspecified** | Less frequent | Tumour lysis syndrome |
| | Frequency unknown | Tumour haemorrhage/tumour necrosis |

| | | |
|---|---|---|
| **(including cysts and polyps)** | | |
| **Blood and lymphatic system disorders** | Frequent | Neutropenia, thrombocytopenia, anaemia, febrile neutropenia |
| | Less frequent | Pancytopenia, bone marrow depression, eosinophilia, lymphadenopathy, lymphopenia, haemolytic anaemia, thrombotic microangiopathy |
| **Immune system disorders** | Less frequent | Anaphylactic shock |
| **Metabolism and nutrition disorders** | Frequent | Anorexia |
| | Less frequent | Dehydration, hyperuricaemia, hypokalaemia, increased appetite, decreased appetite, gout, hypophosphataemia, hyperkalaemia, hyponatraemia, taste disturbances, hyperglycaemia, hypercalcaemia, hypomagnesaemia |
| **Psychiatric disorders** | Frequent | Insomnia |
| | Less frequent | Depression, anxiety, decreased libido, confusion |
| **Nervous system disorders** | Frequent | Headache, dizziness, paraesthesia, ~~insomnia~~, taste disturbance |
| | Less frequent | Cerebral haemorrhage, syncope, peripheral neuropathy, hypoaesthesia, somnolence, migraine, memory impairment, cerebral oedema, increased intracranial pressure, convulsions, sciatica, restless leg syndrome, tremor |
| | Frequency unknown | Cerebral oedema, cerebrovascular accident, transient ischaemic attack, ischaemic stroke |
| **Eye disorders** | Frequent | Conjunctivitis, increased lacrimation, blurred vision |
| | Less frequent | Eye irritation, conjunctival haemorrhage, dry eye, orbital oedema, macular oedema, papilloedema, retinal and |

| | | |
|---|---|---|
| | | scleral haemorrhage, vitreous haemorrhage, glaucoma, blepharitis, cataract, optic neuritis |
| **Ear and labyrinth disorders** | Less frequent | Vertigo, tinnitus, hearing loss |
| **Cardiac disorders** | Less frequent | Cardiac failure/arrest, pulmonary oedema, tachycardia, pericardial effusion, pericarditis, cardiac tamponade, angina pectoris, myocardial infarction, atrial fibrillation, palpitations, dysrhythmia |
| **Vascular disorders** | Less frequent | Haematoma, hypertension, hypotension, flushing, peripheral coldness, thrombosis/embolism, Raynaud's phenomenon, subdural haematoma |
| **Respiratory, thoracic and mediastinal disorders** | Frequent | Epistaxis, dyspnoea |
| | Less frequent | Cough, pleural effusion, pharyngolaryngeal pain, acute respiratory failure, pulmonary fibrosis, interstitial pneumonitis, pharyngitis, pleuritic pain, pulmonary hypertension, pulmonary haemorrhage |
| **Gastrointestinal disorders** | Frequent | Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, abdominal distension, flatulence, constipation, gastro-oesophageal reflux, mouth ulceration |
| | Less frequent | Gastrointestinal haemorrhage, melaena, ascites, gastric ulcer, gastritis, eructions, dry mouth, colitis, diverticulitis, ileus/intestinal obstruction, tumour haemorrhage/tumour necrosis, intestinal perforation, pancreatitis and oropharyngeal pain, colitis, inflammatory bowel disease, gastric antral vascular ectasia (GAVE), stomatitis, oesophagitis, haematemesis, dysphagia |
| | Frequent | Increased hepatic enzymes |

| | | |
|---|---|---|
| **Hepato-biliary disorders** | Less frequent | Jaundice, hepatitis, hyperbilirubinaemia, hepatic failure, hepatic necrosis |
| **Skin and subcutaneous tissue disorders** | Frequent | Periorbital oedema, dermatitis, eczema, rash, face oedema, eyelid oedema, pruritus, erythema, dry skin, alopecia, night sweats |
| | Less frequent | Petechiae, contusion, increased sweating, urticaria, onychoclasis, photosensitivity reaction, purpura, hypotrichosis, cheilitis, skin hyperpigmentation, skin hypopigmentation, psoriasis, exfoliative dermatitis and bullous eruptions, angioedema, vesicular rash, Stevens-Johnson syndrome, acute febrile neutrophilic dermatosis (Sweet's syndrome), ecchymosis, increased tendency to bruise, folliculitis, nail discolouration, leucocytoclastic vasculitis, acute generalised exanthematous pustulosis (AGEP) |
| | Frequency unknown | Palmoplantar erythrodysaesthesia syndrome, lichenoid keratosis, lichen planus, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), pseudoporphyria |
| **Musculoskeletal, connective tissue and bone disorders** | Frequent | Muscle spasm and cramps, musculoskeletal pain, including arthralgia, joint swelling, bone pain |
| | Less frequent | Sciatica, joint and muscle stiffness, avascular necrosis/hip osteonecrosis, muscular weakness, arthritis, rhabdomyolysis/myopathy |
| | Frequency unknown | Growth retardation in children |
| **Renal and urinary disorders** | Less frequent | Acute renal failure, renal pain, increased urinary frequency, haematuria |

| | | |
|---|---|---|
| | Frequency unknown | Chronic renal failure |
| **Reproductive system and breast disorders** | Less frequent | Gynaecomastia, breast enlargement, scrotal oedema, menorrhagia, nipple pain, sexual dysfunction, erectile dysfunction, irregular menstruation, haemorrhagic corpus luteum/haemorrhagic ovarian cyst |
| **General disorders and administration site conditions** | Frequent | Fluid retention and oedema, fatigue, pyrexia, weakness, rigors, chills |
| | Less frequent | Malaise, haemorrhage, anasarca, chest pain |
| **Investigations** | Frequent | Increased weight |
| | Less frequent | Increased blood alkaline phosphatase, increased blood creatinine, decreased weight, increased blood creatine phosphokinase, increased blood lactate dehydrogenase, increased blood amylase |

* Reported mainly from post-marketing experience with Imatinib. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

***Reporting of suspected adverse reactions:***

Reporting suspected adverse reactions after authorisation of **IMATINIB ACCORD** is important. It allows continued monitoring of the benefit/risk balance of **IMATINIB ACCORD**. Health care providers are asked to report any suspected adverse reactions via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

**4.9 OVERDOSE**

*Symptoms*

Severe muscle cramps, elevations of serum creatinine, ascites and elevated liver transaminase levels, and elevations of bilirubin. A general exacerbation of symptoms listed as side effects may be seen in the event of overdosage (see section 4.8).

*Treatment*

Patients should be observed and appropriate symptomatic and supportive treatment given.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacological classification: A.26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents, BCR-ABL tyrosine kinase inhibitors, ATC code: L01EA01

Imatinib is a protein-tyrosine kinase inhibitor, which inhibits the BCR-ABL (Breakpoint cluster region-abelson) tyrosine kinase at the *in vitro* cellular and *in vivo* levels. *In vitro*, the compound selectively inhibits proliferation and induces apoptosis in BCR-ABL positive cell lines as well as fresh leukaemic cell cultures from patients with Philadelphia chromosome positive chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia (ALL) patients. In colony transformation assays using *ex vivo* peripheral blood and bone marrow samples, imatinib shows selective inhibition of BCR-ABL positive colonies from CML patients.

Imatinib is an inhibitor of the receptor tyrosine kinases for platelet derived growth factor (PDGF) and stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated cellular events.

### 5.2 PHARMACOKINETIC PROPERTIES

**Pharmacokinetic properties**

The pharmacokinetics of imatinib have been evaluated over a dosage range of 25 to 1000 mg. Plasma pharmacokinetic profiles were analysed on day 1 and on either day 7 or day 28, by which time plasma concentrations had reached steady state.

*Absorption*

Mean absolute bioavailability is 98 %. The coefficient of variation for plasma imatinib AUC (area under curve) is in the range of 40 – 60 % after an oral dose. When given with a high fat meal, the rate of absorption of imatinib was minimally reduced (11 % decrease in $C_{max}$ and prolongation of $t_{max}$ by 1,5 hours), with a small reduction in AUC (7,4 %) compared to fasting conditions.

*Distribution*

At clinically relevant concentrations of imatinib, binding to plasma proteins was approximately 95 % on the basis of *in vitro* experiments, mostly to albumin and alpha-acid-glycoprotein, with little binding to lipoprotein.

*Biotransformation*

CYP3A4 is the major enzyme responsible for metabolism for imatinib. Other cytochrome P-450 enzymes, such as CYP1A2, CYP2D6, CYP2C9 and CYP2C19, play a minor role in its metabolism. The main circulating active metabolite in humans is a N-demethylated piperazine derivative, formed predominantly by CYP3A4. It shows *in vitro* potency similar to the parent imatinib. The plasma AUC for this metabolite is about 15 % of the AUC of imatinib, and the plasma protein binding is similar to that of the parent compound.

*Elimination*

Elimination is predominantly in the faeces, mostly as metabolites. Based on the recovery of compound(s) after an oral 14C-labelled dose of imatinib, approximately 81 % of the dose was eliminated within 7 days, in faeces (68 % of dose) and urine (13 % of dose). Unchanged imatinib accounted for 25 % of the dose (5 % urine, 20 % faeces), the remainder being metabolites.

*Plasma pharmacokinetics:*

Following oral administration in healthy volunteers, the $t_{½}$ was approximately 18 hours. The increase in mean AUC with increasing dose was linear and dose proportional in the range of 25 – 1000 mg imatinib after oral administration. There was no change in the kinetics of imatinib on repeated dosing, and accumulation was 1,5 – 2,5 fold at steady state when dosed once daily.

**Specific patient groups**

Based on population pharmacokinetic analysis, there was a small effect of age on the volume of distribution (12 % increase in patients > 65 years old). This change is not thought to be clinically significant.

The effect of body weight on the clearance of imatinib is such that for a patient weighing 50 kg the mean clearance is expected to be 8,5 litres/hour, while for a patient weighing 100 kg the clearance will rise to 11,8 litres/hour. These changes are not considered sufficient to warrant dose adjustment based on kg body weight. There is no effect of gender on the kinetics of imatinib.

*Pharmacokinetics in children:*

Imatinib is rapidly absorbed after oral administration in paediatric patients. Dosing in children at 260 and 340 mg/m$^2$ achieved the same exposure, respectively, as doses of 400 mg and 600 mg in adult patients.

*Organ function impairment:*

Imatinib and its metabolites are not excreted via the kidney to a significant extent. Exposure to imatinib may be expected to increase if liver function is impaired. Imatinib should be used with caution in patients with liver impairment (see section 4.4).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Hypromellose

Cellulose microcrystalline

Crospovidone

Colloidal anhydrous silica

Magnesium stearate

*Opadry yellow 03F520050*

Hypromellose

Talc

Macrogol

Iron oxide yellow

Iron oxide red

**6.2 INCOMPATIBILITIES**

Not applicable

**6.3 SHELF LIFE**

3 years

**6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Store at or below 25 °C.

Protect from moisture. Keep blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

**6.5 NATURE AND CONTENTS OF CONTAINER**

**IMATINIB ACCORD** film-coated tablets are packed into clear transparent PVC/PVdC-Alu blisters or plain matt finish Alu-Alu blisters, containing 10 tablets per blister.

Pack size: 20, 30 or 60 film-coated tablets per carton.

**6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING**

No special requirements.

**7. HOLDER OF CERTIFICATE OF REGISTRATION**

Accord Healthcare (Pty) Ltd

Building 2

Tuscany Office Park

6 Coombe Place, Rivonia

Gauteng

South Africa

**8. REGISTRATION NUMBER**

**IMATINIB ACCORD 100**: 49/26/0740

**IMATINIB ACCORD 400**: 49/26/0741

**9. DATE OF FIRST AUTHORISATION**

30 September 2016

**10. DATE OF REVISION OF TEXT**

26 August 2022